## REMARKS

Claims 1, 7, 29, 34-36, and 40 remain pending in the application. In light of the lack of teaching in the prior art as to choline magnesium trisalicylate or its equivalence with other NSAIDS with respect to treatment of neurotrauma, reconsideration of the pending claims consistent with MPEP 2131.02 is respectfully requested.

Claims 1, 7, 29, 34-36, and 40 stand rejected under 35 U.S.C. §103(a) over Grilli et al. (WO 98/20864) in view of Bakhshi et al. (Journal of Neuro Oncology, 26, 133-9), and Myseros et al. (The rationale for glutamate antagonists in the treatment of traumatic brain injury, Ann NY Acad Sci, 1995, 765:262-271) and further in view of McGeer et al. (US 5,192,753).

### Remarks Directed to Rejection of Claims 1, 7, 29, 34-36, and 40 Under 35 U.S.C. §103(a) over Grilli et al. in view of Bakhshi et al. and Myseros et al. and further in view of McGeer et al. (US 5,192,753)

The articulation of the rejection is found in Paper No. 20071107, pages 4-8 and reiterated as the basis of the rejection in the outstanding Paper No. 20080801.

Primarily, the outstanding rejection concludes that all NSAIDS are equivalent and that all NSAIDS "would obviously be non-inhibitory of platelets." (Paper No. 20080801, page 3.) Included in the list of equivalent NSAIDS are acetylsalicylic acid (asprin) ibuprofin, (McGeer) sodium salicylate, and salicylamide (Grilli et al.).

Applicant's primary difference with the outstanding rejection is that all NSAIDS are NOT equivalent with respect to treatment of neurotrama or neural injury when compared to degenerative diseases such as Alzheimer's disease.

To find two or more compounds equivalent, a prima facie case requires that Examiner find that the prior art compounds: (A) perform the function specified in the claim; and (B) are not excluded by any explicit definition provided in the specification for an equivalent. MPEP §2183.

With respect to (A) performing the same function, it must be demonstrated that the prior art element performs the identical function specified in the claim in substantially the same way, and produces substantially the same results as the corresponding element disclosed in the specification. *Kemco Sales, Inc. v. Control Papers Co.*, 208 F.3d 1352, 54 USPQ2d 1308 (Fed. Cir. 2000). (emphasis added)

With respect to (B): a person of ordinary skill in the art must have recognized the interchangeability of the element shown in the prior art for the corresponding element disclosed in the specification. *Caterpillar Inc. v. Deere & Co.*, 224 F.3d 1374, 56 USPQ2d 1305 (Fed. Cir. 2000); *Al-Site Corp. v. VSI Int' l, Inc.*, 174 F.3d 1308, 1316, 50 USPQ2d 1161, 1165 (Fed. Cir. 1999); *Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus. Inc.*, 145 F.3d 1303, 1309, 46 USPQ2d 1752, 1757 (Fed. Cir. 1998); *Lockheed Aircraft Corp. v. United States*, 193 USPQ 449, 461 (Ct. Cl. 1977); *Data Line Corp. v. Micro Technologies, Inc.*, 813 F.2d 1196, 1 USPQ2d 2052 (Fed. Cir. 1987).

Neither of these tests are satisfied by the cited teaching of any of the cited prior art alone or in combination with respect to treatment of neurotrauma as required by the pending claims. In the absence of equivalency of all NSAIDS with respect to neurotrauma, a *prima facie* case of obviousness is not satisfied in the outstanding rejection.

**Standard for a *prima facie* case of obviousness**

The Supreme Court in KSR Int'l Co. v. Teleflex, Inc., 127 S. Ct. 1727 (2007), has recently articulated the standard for establishing whether a claim is obvious over prior art. In KSR the Court reestablished that Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), remains the controlling precedent. Under Graham, to establish a *prima facie* case of obviousness an Examiner must analyze:

(1) the scope and content of the prior art;

(2) the differences between the claimed invention and the prior art; and

(3) the level of ordinary skill in the pertinent art.

Graham, 383 U.S. at 17–18, 148 USPQ at 467.

It is Applicant's understanding that the form and substance of rejections under 35 U.S.C. §103(a) are currently governed by guidelines articulated in the Federal Register, 2007, Vol. 72, No. 195, 56525-56534 therein embodying the test outlined in KSR. These guidelines require a factual inquiry, resolution of ordinary skill in the art to which the invention pertains, and an explicit recitation of the rationale for the rejection as selected from among seven possible bases (identified in the Federal Register with letters A-G). The basis for Applicant's reply is also provided within the Federal Register guidelines.

While the outstanding rejection appears to address the scope and content of the prior art and the differences between the claimed invention and the prior art, the level of ordinary skill in the art is not articulated either expressly or inherently. As such, the outstanding rejection fails to satisfy all elements required for a finding of obviousness as required under the analysis defined

in *Graham* and reaffirmed in *KSR*. Applicant's remarks *infra* address each of the *Graham* elements and the rational for a conclusion of obviousness.

**Resolution of One of Ordinary Skill in the Art**

Part of the *Graham* factual inquiry requires an indication of the level of ordinary skill in the art to which the invention pertains. Within the outstanding Office Action, as such, it is respectfully requested that the level of ordinary skill in the art be stated with greater specificity as the present invention is submitted to require skills beyond those imparted to a single person of ordinary skill in the art. Upon identification of the level of ordinary skill in the art, Applicant reserves the right to make of record additional declarations provided under 37 CFR 1.132 detailing how particular claimed aspects are beyond the scope of various such professional individuals such as a physician or biochemist.

***Graham* Factual Findings and Response Thereto**

The outstanding rejection is based on Grilli et al. teaching the genus of NSAID yet without teaching the claimed species of choline magnesium salicylate. (Paper No. 20071107, page 5 "Grilli et al. lacks a specific teaching of the claimed NSAID-choline magnesium trisalicylate, the mode of administration and a specific teaching of the treatment of neurotrauma associated with traumatic brain injury.")

To support the failings of Grilli et al. to teach choline magnesium trisalicylate, Paper No. 20071107 at page 7 cites McGeer for the proposition that salicyclic acid, acetylsalicyclic acid, choline magnesium trisalicylate, salicylate, etc. are "equivalent NSAIDs useful for the treatment

of Alzehimer's disease (col. 1, linese 36-65.)" Further in support of the belief that all NSAIDs are equivalent the outstanding rejection states: "And furthermore, at the time of the invention all NSAID were assumed to have the same properties because McGeer teaches that Alzheimer's disease can be effectively treated with any drug of the NSAID class (column 2, lines 53-55)." (Paper No. 20080801, page 3).

Perhaps most importantly, no patentable weight is given to the property of choline magnesium trisalicylate being non-inhibitory of platelets.

> This is found not persuasive because non-inhibitory (sic) of platelets is a property of an NSAID such as choline magnesium trisalicylate. And (sic) normally patentability is NOT given to properties of composition. As stated in the previous office action dated 11/13/2007, that (sic) it is known to administer the same compositions as instantly claimed, the compositions would obviously be non-inhibitory of platelets. A compound and its properties are inseparable. *In re Papesch*, 315 F.2d 381,137 USPQ43 (CCPA 1963). (Paper No. 20080801, page 3.)

Applicant agrees that a compound and its properties are inseparable. However, applicant asserts that different compounds that may have a single overlapping property do not necessarily have an entirely overlapping equivalence. This is seen with relation to the instant application by inhibition of cyclooxygenase by both aspirin and ibuprofen whereby aspirin also inhibits platelet activity but ibuprofin does not. Similarly, salicylate and acetylsalicylate both inhibit prostaglandin synthesis by inhibiting cyclooxygenase, however, salicylate requires approxamately 20-fold higher concentration to do so. In contrast, person having ordinary skill in the art recognizes that choline magnesium trisalicylate does not inhibit cyclooxygenase, but does decrease prostaglandin synthesis by an unknown mechanism. (See e.g. Szczeklik A, Eur Respir J., 1990; May;3(5):535-9. Abstract- "There was no significant decrease in serum $TXB_2$

levels, indicating the absence of cyclooxygenase inhibition with CMT.") As such, the knowledge in the art recognizes similarity between choline magnesium trisalicylate and salicylate in their similar inhibition of prostaglandin synthesis, but not by the same mechanism producing different properties.

Further, salicylate and choline magnesium trisalicylate are recognized in the art as entirely different with respect to inhibition of platelet activation as measured by either aggregation or thromboxane $B_2$ synthesis. Aspirin and salicylate both inhibit platelet aggregation. (See Rosenberg, JPET, 1971; 179:410-418) Conversely, a person of ordinary skill in the art recognizes that choline magnesium trisalicylate does not inhibit platelet aggregation. (See Stuart, JJ, Pyharmatherapeutica, 1981; 2(8):547 titled "Choline magnesium trisalicylate does not inhibit platelet aggregation.") Thus, a person of ordinary skill in the art recognizes that the inseparable properties of salicylate and choline magnesium trisalicylate are different and non-overlapping- NOT equal. Since the compounds of Grilli et al. and Myseros are functionally distinguishable and not equal, a person of ordinary skill in the art has no suggestion or motivation from the compounds taught by Grilli et al. or Myseros to use choline magnesium trisalicylate for the treatment of neurotrauma as required by the instant claims.

Applicant incorporates by reference all remarks made of record March 13, 2008 with respect to the failings of each of the cited prior art.

**Rationale for Obviousness**

The Supreme Court and the Court of Appeals for the Federal Circuit are in agreement

that the teaching, suggestion, and motivation test as used by the CAFC is fully consistent with an analysis of obviousness under *Graham*. The Court in *KSR* articulated that "[t]here is no necessary inconsistency between the idea underlying the TSM test and the Graham analysis," and explained that the CAFC has, in many cases, applied the TSM test in accord with the principles of *Graham*. *KSR*, 127 S. Ct. at 1732, 82 USPQ2d at 1396. The Supreme Court also commented that the CAFC "no doubt has applied the test in accord with these principles [set forth in KSR] in many cases." *Id.*

The CAFC has interpreted *KSR* to require an explicit showing of where the prior art suggested making the specific modifications necessary to achieve the claimed invention. As was recently articulated by the CAFC, for a case of *prima facie* obviousness to be found for chemical matter, "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for the change in structure." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty, Ltd.*, 83 USPQ2d 1169, 1174 (Fed. Cir. 2007). The court further made expressly clear that "in order to find a prima facie case of unpatentability in such instances, a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required." *Id.* (quoting *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995) (internal references omitted). The court clarified that this test for chemical compounds is "consistent with the principles enunciated in *KSR*." *Id.* (citing *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007).

This standard was affirmed in *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, where the Federal Circuit continued application of the teaching, suggestion, and motivation test "flexibly applied" so as to require that any *prima facie* case of obviousness must be accompanied by an explicit showing where the relied on prior art provided the requisite teaching,

suggestion, or motivation. 520 F.3d 1358, 1364-65 (Fed. Cir. 2008). The flexible nature of the test allows for a teaching, suggestion, or motivation to arise from knowledge in the art or from a standard desire to improve on prior inventions. However, if the cited prior art is limited to patents and publications as it is in the subject rejection, the teaching, suggestion, or motivation to modify that prior art must be found in the cited art itself. The prior art of record fails to provide, explicitly or inherently, any teaching, suggestion, or motivation that would lead a person having ordinary skill in the art to the instantly claimed invention.

The BPAI also recognized that *KSR* "held that the TSM test must be applied flexibly, and take into account a number of factors 'in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed.'" *Ex parte Whalen II*, Appeal 2007-4423, July 23, 2008, page 15 (citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007)). Further, "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does ... To facilitate review, this analysis should be made explicit." *Id.* Finally, in the face of evidence that a reference teaches away from the claimed invention the BPAI stated "it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition." *Ex parte Whalen II*, Appeal 2007-4423 at 16. Taken in sum, the BPAI recognizes that any *prima facie* case of obviousness must explicitly identify where any of multiple cited prior art provides motivation to combine the references so as to produce the claimed invention. This test is not met by the subject rejection in that the prior art of record fails to provide, explicitly or inherently, any teaching, suggestion, or motivation to combine the references so as to lead a person having ordinary skill in the art to the instantly claimed invention.

The standard set down in *KSR* is fully in line with historical precedent. As supported by the CAFC, there must be an express evidentiary showing of where the prior art provides motivation to combine all elements of the claims. It is a well established legal principle that to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Additionally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). This suggestion or motivation must be made explicit. A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). The cited prior art combination fails each of these requirements.

In support of the above precedents, the Court in *KSR* suggested seven possible rationales for a finding of obviousness. These are captured in the Federal Register, 2007, Vol. 72, No. 195, 56525-56534, which serves as the current basis used by the USPTO for a finding of obviousness. These rationales are reproduced below.

> (A) Combining prior art elements according to known methods to yield predictable results;
>
> (B) Simple substitution of one known element for another to obtain predictable results;
>
> (C) Use of known technique to improve similar devices (methods, or products) in the same way;
>
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
>
> (E) "Obvious to try"—choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

> (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art;
>
> (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

(Federal Register, Vol. 72, No. 195, 57529).

The explanations articulated in Paper Nos. 20071107 and 20080801, lead Applicant to the assumption that the rationale for obviousness corresponds to rationale (A) of the KSR obviousness examination guidelines namely that the Examiner has found all prior art elements that may combined according to known methods to yield predictable results producing the instantly claimed invention. In the event that Applicant's assumption as to the rationale for the rejection is incorrect, it is respectfully requested that the undersigned attorney of record be contacted at the earliest possible convenience so that a response may be provided consistent with the implicit rationale for the finding of obviousness. The requirements for an obviousness rejection based on this rationale are reproduced below.

> To reject a claim based on this rationale, Office personnel must resolve the *Graham* factual inquiries. Office personnel must then articulate the following:
>
> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference;

> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
>
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
>
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

Essential to satisfaction of a *prima facie* case of obviousness under rationale A is that one of ordinary skill in the art would have recognized that the results of the combination were predictable. Predictability must arise from the teachings found in the prior art itself. As eluded to *supra*, for one of ordinary skill in the art to have recognized the predictability of using choline magnesium trisalicylate the compounds disclosed by Grilli et al. must be equivalent with choline magnesium trisalicylate in the treatment of neurotrauma, AND treatment of Alzheimer's disease as per McGreer must be equivalent to treatment of neurotrauma with respect to NSAID function.

Predictability and motivation to combine Grilli et al. and McGeer for its teaching of choline magnesium trisalicylate is cited to arise because:

> One would have been motivated to utilize the specific salicylate choline magnesium trisalicylate because of the expectation of success in treating neuronal damage associated with Alzheimer's disease by administering a derivative of acetylsalicylic acid to a patient in need thereof, as taught by Grilli et al. and due to McGeer

> et al's. demonstration of the equivalence of choline magnesium trisalicylate, acetylsalicylic acid and salicylic acid. (Paper No. 20071107, page 7.)

This is because "McGeer et al. teaches that choline magnesium trisalicylate is a salicylate suitable for the treatment of Alzheimer's disease." *Id.*

Applicant respectfully contends that the disclosed compounds of Gilli et al. or McGeer are not equivalent when used to treat neurotrauma as required by the subject pending claims. For two compounds to be equivalent in the treatment of a disease or injury they must function via the same pathway and have identical side effects so as to produce substantially the same results as the corresponding element disclosed in the specification. A primary consideration for the treatment of neurotrauma is the propensity of bleeding. Thus, it is essential that any compound used to treat neurotrauma not promote increased bleeding as a primary side effect. In contrast, Alzheimer's disease is a degenerative disease that is not associated with a bleeding phenotype. The anti-platelet activity of disclosed compounds in the cited prior art is irrelevant for the treatment of Alzheimer's disease, but is highly relevant for the treatment of neurotrauma. Any predictability from the teaching of McGeer that therein disclosed compounds may be suitable for the treatment of Alzheimer's disease does not equate to predictability for the treatment of neurotrauma. Indeed, no cited teaching of McGeer or any other cited prior art suggests an equivalency between treatment of Alzheimer's disease and treatment of neurotrauma. Thus, there is no explicit showing in the prior art to combine or modify to produce the instantly claimed invention. In the absence of such an explicit showing of equivalency between treatment of Alzheimer's disease and treatment of neurotrauma, no *prima facie* case of obviousness is satisfied.

Unlike the sodium salicylate and salicylamine of Grilli et al., and aspirin of McGeer, choline magnesium trisalicylate has properties that render it suitable for the indication of neurotrauma (i.e. non-inhibition of platelets and protective effects of magnesium ions). While all NSAIDs have anti-inflammatory properties that render them operable for treatment of Alzehimer's disease as per McGeer, all NSAIDs are NOT interchangeable with respect to treatment of neurotrauma as required by the subject claims. Specifically, the NSAIDs articulated in Grilli et al. (page 1, line 1- page 3, line10) are largely inhibitory of platelet clotting thereby rendering them wholly unacceptable for the indications of the pending claims in which cerebral bleeding is associated with neurotrauma. As controlling bleeding is a primary consideration in the treatment of neurotrauma, a person of ordinary skill and the art would have no motivation to use the teaching of Grilli alone or in combination with McGeer in that neither of these references adequately address the bleeding concern. Indeed, if a person of ordinary skill in the art were to rely on the teaching of Grilli et al. and McGeer this reliance would likely result in a **fatal** patient outcome with respect to neurotrauma. As such, a person of ordinary skill and the art has no motivation to use the teachings of Grilli et al. or McGeer alone or in combination because the compounds do not produce substantially the same results when used for the treatment of neurotrauma as required for a demonstration of equivalency.

The administration of aspirin to a subject suffering neurotrauma would cause additional harm through perpetuating cerebral bleeding by platelet inhibition. (See instant specification page 9, lines 1-22). With respect to the pending claims there is no equivalency with aspirin and instead a contra-indication. McGeer is specifically cited as teaching equivalency of aspirin and choline magnesium trisalicylate. (See col. 1, lines 62-65.) However, with respect to bleeding

propensity aspirin and choline magnesium trisalicylate do not produce substantially the same results particularly when used for the treatment of neurotrauma and are as such not equivalents.

The test outlined in rational A of the Federal Register, or any other rational, is respectfully submitted to have not been met by the subject rejection of the pending claims as each reference individually fails to provide, explicitly or inherently a reason to use choline magnesium trisalicylate from among the large number of compounds within the genus of NSAIDs to treat inflammation in neurotrauma. As such, there is no teaching, suggestion or motivation to lead a person having ordinary skill in the art to the instant claimed invention needed to sustain a *prima facie* case of obviousness. Rather, the outstanding rejection resorts to motivation derived from the treatment of **entirely non-analogous** degenerative neurological condition with a generic NSAID per McGeer, without any teaching, suggestion, or motivation as to the claimed route for achieving this objective, the indication of neurotrama or the properties of CMS that make this treatment operative while other apparently equivalent NSAIDs (e.g. aspirin) would be lethal. Given the numerous art recognized differences between Alzheimer's disease, tumors, and neurotrauma one of ordinary skill and the art would not be able to predict success from combining the teachings of Gilli et al. and McGeer because these references, and the other references of the outstanding rejection, do no teach or suggest how the NSAIDS disclosed therein will effect patient outcome following neurotrauma.

Applicant's reference to MPEP 2131.02 is respectfully submitted to be relevant to understanding the teachings of Grilli et al. as to the compounds taught to be useful in treating inflammation associated with neurodegenerative disease. Applicant notes agreement with the Examiner that Grilli et al. in view of Bakhshi et al. and Myseros et al. "lack a teaching of choline

magnesium trisalicylate" (paragraph two on page 7 of the Paper No. 20070416). As such, the structures of NSAIDs taught in these references are not those being claimed and further the indications taught in Grilli et al. in view of Bakhshi et al. and Myseros et al. and further in view of McGeer et al. are not concerned with bleeding associated with neurotrauma.

With respect to the other prior art references, these fail to bolster the failings of Grilli et al. or McGeer. The Bakhshi et al. teaching of administration of CNS drugs via intrathecal catheter does not reach to the pending claims in terms of delivery of choline magnesium trisalicylate for the treatment of neurotrauma and instead discloses the application of the intrathecal catheter in the treatment of CNS tumors (Abstract) and with special emphasis on brain tumors. Similar to Alzheimer's disease, treatment of a tumor lacks the immediacy of neurotrauma and indeed would be disfavored by one of skill in the art as overly invasive when NSAIDs are tailored to promote oral and intravenous bioavailability across the blood-brain barrier.

Myseros et al. similarly lacks a teaching relevant to the equivalence of choline magnesium trisalicylate with the compounds of Grilli et al.. As such, Myseros fails to bolster the failings of the other cited prior art.

In view of the above remarks, reconsideration and the withdrawal of the rejection of claims 1, 7, 29, 34-36, and 40 under 35 U.S.C. §103(a) over Grilli et al. in view of Bakhshi et al. and Myseros et al. and further in view of McGeer et al. is respectfully solicited.

## Summary

Claims 1, 7, 29, 34-36, and 40 are the claims pending in this application. Each claim is believed to be in proper form and directed to allowable and patentable subject matter. Reconsideration and allowance of the claims is requested. Should the Examiner find to the contrary, he is respectfully requested to contact the undersigned attorney in charge of this application to resolve any remaining issues.

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Respectfully submitted,

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